## REMARKS

The present invention relates to methods for the treatment of acquired immune deficiency syndrome (AIDS). Claims 42, 45, 46 and 48-50 are pending in the present application. Claims 45 and 48-50 have been withdrawn from consideration without prejudice to the inclusion of the subject matter contained therein in any later filed divisional or continuation applications. Claim 46 been amended herein. Support for the amendment to claim 46 is discussed in more detail below.

Withdrawn Rejection to Claims 42 and 46 Under 35 U.S.C. §112, First Paragraph

Applicants acknowledge and appreciate the withdrawal of the rejection of claims 42 and 46 under 35 U.S.C. §112, first paragraph.

Priority Date

Applicants acknowledge that the present application claims its earliest priority date from U.S. Patent Application No: 08/771,831, filed December 23, 1996, now issued as U.S. Patent 5,888,511.

Rejection of Claim 46 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claim 46 under 35 U.S.C. §112, first paragraph for lack of written description. More particularly, the Examiner contends that the specification does not contain sufficient written description for the term "allelic and species variants thereof" because, in the Examiner's view, the relevant identifying characteristics, such as structure or other physical or chemical characteristics are not set forth in the specification as filed. The Examiner has cited Skolnick et al. (2000, Trends in Biotech., 18: 34-39), Lederman et al. (1991, Molecular Immunology 28: 1171-1181) and Li et al. (1980, Proc. Nat'l. Acad. Sci. USA) in support of the present rejection.

Applicants, while not wishing to acquiesce with the Examiner's position, but rather in a good faith effort to expedite the prosecution of the present application, have amended claim 46 such that the present claim recites an antibody selected from the group consisting of a monoclonal antibody, a polyclonal antibody, combinations thereof, and a biologically active

fragment, wherein the biologically active fragment is a fragment of an antibody and binds gamma interferon, alpha interferon or tumor necrosis factor alpha. Applicants respectfully submit that the present amendment overcomes the rejection of claim 46 pursuant to 35 U.S.C. §112, first paragraph for lack of written description. Reconsideration and withdrawal of the present rejection is respectfully requested.

Objection to Claim 46

The Examiner has objected to claim 46 in that the term "alleleic" is misspelled and should be spelled "allelic". Applicants submit that the amendments detailed above render the objection to claim 46 moot with respect to this claim and should be withdrawn.

Rejection of Claim 46 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 46 pursuant to 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, the Examiner asserts that claim 46 is indefinite because the antecedent basis of the term "allelic or species variant thereof" is unclear and confusing.

Applicants respectfully submit that the amendment to claim 46 discussed above renders the present rejection of claim 46 under 35 U.S.C. §112, second paragraph, moot, and as such, should be withdrawn.

The Examiner has also rejected claim 46 pursuant to 35 U.S.C. §112, second paragraph, as being indefinite, particularly in that the singular form "biologically active fragment" lacks proper antecedent basis to the plural form of "biologically active fragments".

Applicants have amended claim 46 herein to recite "biologically active fragment" in the singular form and provide antecedent basis for the second recitation of "biologically active fragment" in claim 46. Support for the singular form of biologically active fragment can be found throughout the copy of the Substitute Specification filed December 6, 2002, particularly at page 22, line 16 and at page 25, line 14, and thus the present amendments add no new matter.

Applicants submit that the present amendments overcome the rejection to claim 46 under 35 U.S.C. §112, second paragraph, and reconsideration and withdrawal of the rejection to claim 46 is respectfully requested at this time.

Rejection of Claims 42 and 46 Under 35 U.S.C §103(a)

The Examiner has rejected claims 42 and 46 pursuant to 35 U.S.C. §103(a) as being unpatentable over Mak (U.S. Patent No. 6,190,691) and Skurkovich et al. (1994, Medical Hypotheses 42: 27-35; Skurkovich) in further view of Bucala et al. (International Publication No.: WO 94/26307; Bucala). The Examiner contends that Mak teaches that a number of cytokines, including interferons and tumor necrosis factors contribute to inflammation, that the inflammation can be regulated by anti-inflammatory drugs, and further teaches methods of treating AIDS or HIV positive patients with anti-TNF alpha antibodies. The Examiner also states that Mak differs from the claimed invention by not disclosing the use of anti-gamma interferon antibodies in combination with anti-TNF alpha antibodies to AIDS or HIV infected patients. The Examiner asserts that Skurkovich teaches the use of an antibody to alpha interferon and gamma interferon as a method of treatment, and that in the section entitled Conclusions and Practical Recommendations, Skurkovich teaches neutralizing alpha interferon, gamma interferon and tumor necrosis factor alpha for treating AIDS. The Examiner states that although Skurkovich teaches removing alpha interferon, gamma interferon and tumor necrosis factor alpha via absorbents, the reference differs from the claimed invention by not explicitly teaching administration of antibodies to alpha interferon, gamma interferon and tumor necrosis factor to HIV infected patients *per se*. The Examiner asserts that Bucala teaches methods of treating various conditions involving cytokine mediated toxicity by administering combinations of cytokine-mediated toxicity antagonists, including anti-TNF alpha and anti-gamma interferon. From this, the Examiner opines that is would have been obvious to one of skill in the art to apply the teachings of Mak and Skurkovich to target and neutralize alpha interferon, gamma interferon and tumor necrosis factor in AIDS or HIV infected patients by administering a combination of antibodies to alpha interferon, gamma interferon and tumor necrosis factor. The Examiner, also states that it would be *prima facie* obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose in order to form a third composition that is used for the same purpose. *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980). Applicants respectfully traverse this rejection.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant

matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

None of these criteria have been met here.

Mak fails to provide any suggestion or motivation to modify or combine the reference teachings to arrive at the present invention. Contrary to the Examiner's assertions, Mak does not teach administrating antibodies to tumor necrosis factor alpha to treat HIV infection or AIDS. Mak teaches that an anti-TNF alpha antibody was used to treat inflammatory bowel disease (IBD) and rheumatoid arthritis, but only teaches that TNF is a mediator in the cachexia associated with AIDS and cancer (column 2, lines 34-38), not that AIDS can be treated with an antibody to TNF alpha. Further, Mak teaches that TNF overproduction is seen in AIDS and HIV infection (column 9, lines 16-25 and lines 63-67 respectively), but teaching that TNF alpha is present in AIDS and HIV infected patients is decidedly not the same as teaching that the administration of anti-TNF alpha antibodies can be used to treat AIDS. In fact, such teachings can at best can be classified as "obvious to try", which the Court of Appeals for the Federal Circuit enunciated as a standard insufficient to establish a *prima facie* case of obviousness. *In re O'Farrell*, 853 F.2d 894 at 903 (Fed. Cir. 1988).

Further, in the sole instance in which Mak teaches a method of treating AIDS, the only suggestion is to administer a calcium channel blocker (column 38, lines 60-64). So while the Examiner states that Mak differs from the claimed methods by not disclosing the use of anti-interferon antibodies in combination with anti-TNF antibodies to treat AIDS or HIV infection, Applicants assert that the failings of Mak go far beyond this, and that Mak actually fails to teach the administration of antibodies to TNF alpha to treat AIDS.

Mak further fails to provide the skilled artisan with a reasonable expectation of success in arriving at the present invention. As set forth at column 3, lines 30 to 35, Mak teaches "...methods of treating a pathological condition mediated by TNF production in a mammal by administering a therapeutically effective amount of a potassium sparing diuretic, antidiarrheal, cyclic AMP modulating agent or a calcium channel blocker...". None of these proposed therapies is an antibody to TNF alpha, and there is no reason for the skilled artisan to believe, when armed with the disclosure and data set forth by Mak, that an antibody to TNF alpha will work as part of a treatment for AIDS. In fact, Mak teaches that anti-TNF antibody can be used to treat the chronic inflammation of rheumatoid arthritis and IBD, but in the next paragraph, Mak teaches that the available anti-inflammatory drugs "produce cytotoxic events", "kill cells indiscriminately", "manifest significant adverse effects", and "induce the development of severe side effects" (column 2, lines 39-51). Thus, Mak implies that anti-inflammatory drugs such as anti-TNF alpha antibodies are so rife with danger for the patient, they should not be used. This does not provide a reasonable expectation of success in treating AIDS with anti-TNF alpha antibodies, but actually cautions against it.

In sum, Mak fails to teach the administration of antibodies to TNF alpha to treat AIDS or HIV infection, but rather teaches the administration of calcium channel blockers. Further, Mak teaches that administration of anti-inflammatory drugs, other than diuretics, antidiarrheals, cAMP modulating agent or calcium channel blockers, will lead to adverse events in the patients and admonishes against such treatments.

Skurkovich fails to correct the defects in Mak because Skurkovich does not provide the requisite suggestion or motivation to combine or modify the teachings of Mak, and Skurkovich does not sufficiently provide a reasonable expectation of success to overcome the failings of Mak.

As stated above, application of the "obvious to try" standard is impermissible, and does not sufficiently provide the three criteria necessary to establish a *prima facie* case of obviousness. The Court of Appeals for the Federal Circuit has set forth two situations in which "obvious to try" does not meet the standards of 35 U.S.C. §103(a). They are summarized as follows:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible

> choices until one possible arrives at a successful result, where the prior art gave either no indication of which parameters were critical or not direction as to which of many possible choices is likely to be successful. [Citations Omitted]. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. [Citations Omitted] *In Re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)

Skurkovich teaches that, "In some conditions abIFN, IFNγ and, more rarely, IFN β can be removed, possibly alone or in different combinations from the circulation, joints (RA) or, if present, from the cerebrospinal fluid". Further, in specific reference to AIDS, Skurkovich teaches, "an attempt could be made to remove these two IFNs together with TNF and some autoantibodies and autoantigens (antigens) (page 31, column 2, second paragraph, emphasis added). These teachings squarely fit into both situations when a reference does not meet the requirements of 35 U.S.C. §103(a), and is instead "obvious to try".

In treating AIDS and other autoimmune diseases, Skurkovich teaches the removal of abIFN (aberrant interferon), gamma interferon, beta interferon, TNF, autoantibodies and autoantigens "possibly alone or in different combinations". This amounts to six substances that can be removed from a patient with AIDS, and when removed alone or in different combinations, amounts to 720 (6!) different possibilities, assuming that only one autoantigen or autoantibody is specified and removed. This results in a situation where all the parameters are varied or each of numerous possible choices are attempted until a successful result is reached, one of the hornbook definitions of "obvious to try".

Further, Skurkovich demonstrates that neutralization of antibodies plays a role in the treatment of autoimmune diseases, and while the Federal Circuit might view this as an invitation to explore a new technology or general approach that seems to be promising, there is insufficient guidance to take the teachings of Skurkovich beyond a general approach. The skilled artisan cannot be expected to assemble 720 patients, not counting control subjects, and attempt every conceivable combination of therapy suggested in the reference with any expectation of success. Thus, Skurkovich at best provides an invitation to try the present invention, but this is not sufficient to correct the defects of Mak or to render the present

invention obvious.

Even if the teachings of Skurkovich provide the requisite motivation to combine the reference teachings, no reasonable expectation of success can be gleaned from the teachings of this particular reference. The present invention discloses a method of treating AIDS comprising administering antibodies to gamma interferon, TNF alpha and alpha interferon. However, Skurkovich teaches that "repeated administration of AB [antibodies] (produced in animals) to IFNs is impractical...". The present invention teaches the administration of two antibodies to interferon in addition to an antibody to TNF alpha, but Skurkovich teaches that this would be impractical. So not only does Mak fail to teach administration of an antibody to TNF alpha to treat AIDS, Skurkovich teaches that such administration would be impractical. The combination of the references therefore does not provide a suggestion or motivation to combine the references, and offers no reasonable expectation of success, and therefore does not meet the criteria to render the present invention obvious.

The Examiner has cited Bucala as teaching methods of treating various conditions involving cytokine-mediated toxicity by administering combinations of therapies such as anti-TNF alpha and anti-gamma interferon antibodies. Applicants respectfully assert that Bucala teaches that antibodies to TNF alpha and gamma interferon are insufficient to treat conditions involving cytokine-mediated toxicity, and there is no motivation to combine Bucala with Mak and Skurkovich, and there also lacks a reasonable expectation of success if the references were combined.

Bucala teaches that migration inhibitory factor (MIF) plays a role in shock and inflammation, and inhibition of MIF may be used as a treatment for cytokine-mediated cytotoxicity, shock, inflammation, graft versus host disease and autoimmune disease (page 7, lines 7-14). Bucala also teaches that administration of TNF alpha antibodies may be difficult or inadequate for the treatment of cytokine-mediated cytotoxicity in conditions such as septic shock. Specifically, Bucala teaches that after a bolus endotoxin challenge, TNF alpha quickly peaks and declines just as rapidly, and that TNF alpha antibodies would ideally be present during this brief zenith and nadir of TNF alpha production. However, due to the short time period of the therapeutic window, "the timely delivery of anti-TNFα based therapeutics may be very difficult to achieve clinically" (page 4, lines 12-27). Thus, Bucala teaches that the administration of anti-

TNF alpha antibodies may not be sufficient for the treatment of septic shock, and gives no other reason to believe that they may function in any other cytokine mediated cytotoxicity event, let alone AIDS.

Moreover, Bucala teaches that even if anti-TNF alpha antibodies could be administered to a patient in a timely manner, they are not necessary because the inhibition of MIF is far superior. Bucala teaches that even with the administration of exogenous TNF alpha, anti-MIF therapy is efficacious. This is compared to the rapidly declining levels of TNF alpha in post-acute septic shock, which Bucala previously teaches anti-TNF alpha antibodies do not adequately teach (page 18, lines 5-32). Thus, Bucala actually teaches that inhibition of MIF is preferable to inhibition of TNF alpha with antibodies, and thus, there is no motivation to use anti-TNF alpha antibodies, and consequently there is no motivation or suggestion to combine the teachings of Mak, Skurkovich and Bucala to arrive at the present invention.

Bucala similarly fails to provide a reasonable expectation of success in arriving at the present invention, and accordingly also fails to correct the defects of the Mak and Skurkovich. The Examiner states that Bucala teaches the administration of anti-TNF alpha and anti-gamma interferon antibodies to treat conditions involving cytokine mediated cytotoxicity. However, Bucala does not teach the use of these antibodies alone, and expressly teaches that these antibodies must be combined with a MIF inhibitor to achieve an effective result. On page 42, beginning at line 11, Bucala teaches that MIF inhibitors may be administered alone or in combination with other therapies, such as anti-lipopolysaccharide (LPS), various antibodies to cytokines, as well as steroids, glucocorticoids and IL-10. The common theme running throughout these proposed therapies is that an MIF inhibitor is included in every proposed therapeutic regimen. This teaching is again repeated in Claim 27 on page 115. Further, as stated before, Bucala teaches that MIF inhibitors have properties that inhibitors of TNF alpha do not have, and are thus superior. As an example, Bucala teaches that anti-MIF compounds can be administered after the period in which TNF alpha inhibitors are effective (page 42, lines 27-29) and that anti-TNF alpha antibodies may be clinically difficult to use (page 4, lines 25-27). Thus, Bucala teaches that any combination therapy is lacking as a therapeutic unless it includes an MIF inhibitor. The skilled artisan, armed with the teaching of Bucala, would thus have no reasonable expectation of success in treating any disease involving cytokine dysregulation unless that

treatment included some sort of MIF inhibitor.

For the reasons stated above, Mak and Skurkovich in view of Bucala fail to meet the criteria necessary to establish a *prima facie* case of obviousness, and Applicants respectfully request reconsideration and withdrawal of the rejection of claims 42 and 46 pursuant to 35 U.S.C. §103(a).

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 42 and 46 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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April 23, 2004
(Date)

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